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COMMENTARY

Positioning Europe for the EPITRANSCRIPTOMICS challenge

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ABSTRACT

The genetic alphabet consists of the four letters: C, A, G, and T in DNA and C,A,G, and U in RNA. Triplets of these four letters jointly encode 20 different amino acids out of which proteins of all organisms are built. This system is universal and is found in all kingdoms of life. However, bases in DNA and RNA can be chemically modified. In DNA, around 10 different modifications are known, and those have been studied intensively over the past 20 years. Scientific studies on DNA modifications and proteins that recognize them gave rise to the large field of epigenetic and epigenomic research. The outcome of this intense research field is the discovery that development, ageing, and stem-cell dependent regeneration but also several diseases including cancer are largely controlled by the epigenetic state of cells. Consequently, this research has already led to the first FDA approved drugs that exploit the gained knowledge to combat disease. In recent years, the ~150 modifications found in RNA have come to the focus of intense research. Here we provide a perspective on necessary and expected developments in the fast expanding area of RNA modifications, termed epitranscriptomics.

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Epitranscriptomics, an expanding research area with great potential for biomedicine, biotechnology and crop production.

In contrast to DNA modifications, nucleotide modifications in RNA are far more diverse and abundant, with more than 140 modifications known to date. Modifications in RNA can change the coding of messenger RNAs (mRNAs) and therefore diversify genetic information. Most RNA modifications cannot be identified by traditional sequencing methods. Thus, despite huge investments in RNA Seq, we are still missing an important layer of cellular diversity. Modifications can also affect the processing/splicing, localization, stability, turnover, or translation of mRNAs. Importantly, RNA modifications can be applied transiently, allowing a fast response to changing cellular or environmental conditions. Lastly, similar to the findings of epigenetics research in DNA, groups of proteins have been identified that specifically recognize and bind modified nucleotides thereby affecting the fate of RNA.

Not all RNA modifications can be synthesized by the organisms in which they are found, but can be delivered as a nutrient by the microbiome, therefore regulating host-microbe interactions. Revealing the mechanisms of specific uptake of these chemical "precursors" and their installation as RNA modifications will not only provide information on the metabolism of these substances and cellular pathways, but likely reveal new diseases linked to the machineries involved. RNA modification can also be involved in cell-to-cell horizontal transfer of information mediated by extracellular vesicles.

Most importantly, changes in RNA modifications have been recognized as being the cause of several diseases ranging from immune disorders, over neuromuscular defects, to cancer. Already this knowledge is used and methods that aim at redirecting specific modifications to clinically relevant sites are being tested.

Thus, today, 30 years after the advent of molecular research in epigenetics, we anticipate a similar, if not bigger explosion in Epitranscriptome research with even a larger impact on biomedical, pharmaceutical, livestock, and agricultural developments.

International development: A wakeup call for Europe

Indeed, several countries have already recognized the potential impact of this new research area. For instance, the NIH in the USA has opened two specialized calls to explore the *impact of the epitranscriptome on cancer* (https://grants.nih.gov/grants/guide/pa-files/PA-16-177.html) and *on brain development* (https://grants.nih.gov/grants/guide/pa-files/PAR-17-152.html).

Similarly, Germany has one running and one starting joint research project on the *Chemical Biology of Epigenetic Modifications* and *Chemical Biology of native Nucleic Acid Modifications*, to name a few. The large interest in epitranscriptome research is also reflected by the number of reviews on this topic in the major scientific journals, now almost appearing on a monthly basis.

Thus the international development makes it clear that Epitranscriptome research is an emerging field with high potential. With some international and many national institutions rushing ahead, it is of utmost importance for European science development to establish coordinated funding at the European level.

A COST Action consortium on the Epitranscriptome termed "EPITRAN" (European Epitrancriptomics Network) has already been launched in 2017 with the aim to coordinate a synergistic network of Epitranscriptome research at the European level and to generate the awareness required to acquire European funding on this topic. It currently counts 26 member states and 60 management members. Already in its first year, three networking events are being organized.

The impact of a coordinated European Epitranscriptome network

Coordinated European Epitranscriptome research will affect health, wealth, nutrition and the environment within Europe. The dramatic increase in the number of diseases shown to be linked to changes in RNA modifications indicates major impact in virtually all fields of life and health science. Developing novel methods for the detection of modification patterns or tools for the manipulation of relevant modifications will provide the basis for the development of new diagnostics and therapeutics. Here we list the most prominent areas already known to be impacted by RNA modifications where an obvious profit from increased efforts in R&D is foreseeable:

Biomarkers, diagnostics & personalized medicine

- The recognition that cellular differentiation, cancer but also specific diseases of the immune or the neuromuscular system are associated with or even caused by altered RNA modifications indicates that improved tools for the detection of epitranscriptomic marks as biomarkers will be of great diagnostic value.
- Altered mitochondrial tRNA modifications are a frequent underlying cause of neuromuscular disorders. Future therapies will rely on the targeted restoration of missing or misplaced marks.
- Changes in cytoplasmic tRNA modifications are disease related and a frequent cause of neuropathies such as ALS or epilepsy. These can be used for diagnostics and as specific targets for novel therapies.

Drug development

- Understanding the machineries and factors that introduce, remove, or read RNA modifications will allow their inhibition by the development of novel drugs with pharmaceutical value (e.g. novel antibiotics, antifungal, anti antiprotozoal therapies).
- Changes in the modification patterns of transformed cells can be exploited to develop specific and personalized drugs, e.g. drags that target the "cancer ribosome".
- Elucidating the type, distribution, and occurrence of epitranscriptomic modifications in pathogens and their hosts will allow the development of novel vaccines or antibiotics.

- RNA modifications will be important to bypass resistance against existing antibiotics but also to develop novel antibiotics.
- Site directed removal or addition of modifications can be used to affect the fate and coding potential of therapeutically important RNAs.
- Similarly, undesired immune responses against nucleic acids can be shielded by applying the appropriate modifications to facilitate nucleic acids based therapies.

Agriculture

- A better understanding of the proteins that read the epitranscriptomic marks will provide opportunities for breeding of more resilient crops. For example, the transcripts from a particular set of genes may always be "tagged" by an epitranscriptomic mark, but whether this causes preferential translation, storage or degradation could be dependent on modifications to the readers which could take place within seconds of an environmental stress signal.
- From an environmental perspective it is clear that altered modifications can be found associated with stress responses and altered environmental conditions. In times where climates are becoming more extreme and crops need to be more resistant, RNA modifications will become an important factor for the understanding but also manipulation of stress response, both in plants and in metazoan systems.

Nutrition

- Given that precursors of modifications are provided through nutrients, translational efficiency and fidelity can be affected by directed alteration of nutrients.

Biotechnology

- Improved sequencing technologies will allow Biotech companies to explore new markets for the detection of epitranscriptomic marks.
- Orthogonal translation for the specific labeling or generation of novel proteins may be further developed by expanding the ribosomal and tRNA modification repertoire.
- Biotechnology will profit from the development of improved protein translation machineries by manipulating both ribosomes and mRNAs.

RNA modifications will be used to develop improved biotechniques for synthesis and analysis of RNA molecules.

European excellence

- Concentrating excellent Epitranscriptome research in Europe will not only create a world-leading scientific research community on this topic, but also lead to the establishment of new startups and attract industrial partners, e.g. pharmaceutical companies, thereby creating a large number of jobs in this industry.

Outlook

It is clear that a new era of research on RNA modifications has already begun. Europe needs to concentrate forces in a synergistic manner by coordinating efforts of the leading groups in this field, so as to catch up with other worldwide research initiatives. It is already foreseeable that this Epitranscriptomic era will change our understanding of many aspects of biology, biomedicine, agriculture, and ecology. Importantly, new standardized tools for epitranscriptome research but also standardized bioinformatics solutions have to be developed with biotechnology companies and software developers to allow comparable and compatible research outcomes and dissemination of high-throughput data. Similarly, links with pharmaceutical and agricultural industries need to be strengthened to allow translation of the gained knowledge into biomarker development, diagnostics, drug development, and novel crop production.

Joint research projects will enable Europe to stay ahead of these novel developments, tackle upcoming research challenges, and provide appropriate trainings for a new generation of scientists, pharmaceutical and agricultural researchers. Coordinated research efforts will therefore allow Europe to take maximum advantage of novel developments and therefore position itself as a leader in the development of novel biomarkers, therapies, and nutrients.

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